REMARKS

This responds to the Final Office Action dated October 27, 2009.

Claims 69, 70 and 71 have been added. Accordingly, claims 35-71 are now pending in the application. However, the Examiner has withdrawn claims 51-56 from examination as a result of the restriction requirement. Accordingly, claims 35-50 and 57-71 are now under examination.

Support exists throughout the specification for the subject matter of new claims 69, 70 and 71, for example, at page 4, lines 20-29; at page 18, line 23 to page 19, line 4; and at page 19, lines 22-23.

Applicants submit that no new subject matter has been added to the application.

The Rejection of Claims under § 112

Claims 58-60, 62 and 67-68 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. The Examiner has rejected product claim 58 and composition claims 59-60, 62, 67 and 68. These rejections are addressed separately below.

Product Claim 58

The Examiner asserts that is unclear how the 3,11 b-*cis*-dihydrotetrabenazine of claim 35 can consist of less than 100% of 3,11 b-*cis*-dihydrotetrabenazine, and that the skilled artisan would not be reasonably apprised of what constitutes 3,11 b-*cis*-dihydrotetrabenazine consisting of, for example, 91% 3,11 b-*cis*-dihydrotetrabenazine.

Claim 58 is drawn to the 3,11b-*cis*-dihydrotetrabenazine or a salt thereof according to claim 35, which consists of greater than 90% 3,11b-*cis*-dihydrotetrabenazine, or a salt thereof. Claim 58 depends from claim 35.

Applicant submits that claim 35 is drawn to 3,11b-*cis*-dihydrotetrabenazine (or salts thereof) in all amounts, and/or any amount. Thus, if the 3,11b-*cis*-dihydrotetrabenazine (or salts thereof) was present in 10%, 30%, 50%, or some other percentage, whether in a solution or dry mixture (or some other form), claim 35 would still embrace that solution or dry mixture (or that other form). In other words, claim 35 is not limited to 100% 3,11b-*cis*-dihydrotetrabenazine (or

salts thereof). Any amount of 3,11b-*cis*-dihydrotetrabenazine (or salts thereof) is embraced by claim 35.

It is proper to recite a smaller range in a claim that depends from a broader range.

> [I]t is not improper under 35 U.S.C. 112, second paragraph, to present a dependent claim that sets forth a narrower range for an element than the range set forth in the claim from which it depends. For example, if claim 1 reads "A circuit … wherein the resistance is 70-150 ohms." and claim 2 reads "The circuit of claim 1 wherein the resistance is 70-100 ohms.", then claim 2 should not be rejected as indefinite.
> M.P.E.P. § 2173.05(c)(I).

Therefore, it is completely proper and appropriate to claim an amount or percentage of 3,11b-*cis*-dihydrotetrabenazine (or a salt thereof) that is less than 100%, for example, in claim 58, which depends from claim 35. Accordingly, the subject matter of claim 58 is definite and this rejection under 35 U.S.C. §112, second paragraph, should be withdrawn.

Composition claims 59, 60, 62, 67 and 68

The Examiner makes similar assertions with respect to claims 59, 60, 62, 67 and 68. In particular, the Examiner asserts that the language of these claims is unclear and that one of ordinary skill in the art would not be able to ascertain the metes and bounds of a composition comprising 3,11 b-*cis*-dihydrotetrabenazine or a salt thereof wherein said 3,11 b-*cis*-dihydrotetrabenazine consists of less than 100% 3,11b-*cis*-dihydrotetrabenazine or a salt thereof.

Claim 59 is drawn to a composition comprising 3,11b-*cis*-dihydrotetrabenazine, or a salt thereof, and a pharmaceutically acceptable carrier, wherein the 3,11b-*cis*-dihydrotetrabenazine, or a salt thereof, consists of greater than 90% 3,11b-*cis*-dihydrotetrabenazine, or a salt thereof.

Claims 60, 62, 67 and 68 depend ultimately from claim 59. Claim 60 recites that the composition of claim 59, contains less than 5% of 3,11b-*trans*-dihydrotetrabenazine. Claim 62 recites that the 3,11b-*cis*-dihydrotetrabenazine is a 2*S*,3*S*,11b*R* isomer having the formula (Ia), or a salt thereof. Claim 67 recites that the 3,11b-*cis*-dihydrotetrabenazine, or a salt thereof is in the form of an acid addition salt, and claim 68 defines the salt of claim 67 as a methane sulphonate salt.

Applicants remind the Examiner that claim 60 recites that the *composition* of claim 59 contains less than 5% of 3,11b-*trans*-dihydrotetrabenazine. As the Examiner knows, the term

"comprising" is an open-ended term. Therefore, a *composition comprising* 3,11b-*cis*-dihydrotetrabenazine can clearly contain other components, including some 3,11b-*trans*-dihydrotetrabenazine. Hence, the language of claim 60 is clear and definite without amendment. As currently drawn, it defines the *composition* and some of the components of that composition. No ambiguity exists. Applicants therefore request withdrawal of this rejection under 35 U.S.C. §112, second paragraph, with respect to claim 60.

Claim 62 depends from composition claim 59 and recites that the 3,11b-*cis*-dihydrotetrabenazine is one type of 3,11b-*cis*-dihydrotetrabenazine isomer. As Applicants' specification describes, the 3,11b-*cis*-dihydrotetrabenazine is a mixture of *cis*-isomers (see, page 6, line 7 to page 8, line 18). The composition of claim 59 is directed to all such 3,11b-*cis*-dihydrotetrabenazine isomers. As directed by the M.P.E.P., it is proper for a claim that depends from an independent claim (e.g., claim 59) to be drawn to one or more of the compounds embraced by the independent claim.

> Genus, subgenus, and Markush-type claims, if properly supported by the disclosure, are all acceptable ways for applicants to claim their inventions. They provide different ways to present claims of different scope. M.P.E.P. § 2173.05(h)(I).

Therefore, claim 62 is properly drawn to an isomer of 3,11b-*cis*-dihydrotetrabenazine and Applicants respectfully request withdrawal of this rejection under 35 U.S.C. §112, second paragraph, of claim 62.

Claims 67 and 68 depend ultimately from composition claim 59 and are drawn to an acid addition salt, and a methane sulphonate salt, respectively. Claim 59 is drawn *inter alia* to a composition comprising 3,11b-*cis*-dihydrotetrabenazine. As described above, a dependent claim can embrace a smaller scope or genus than the independent claim from which it depends. Accordingly, claims 67 and 68 are properly drawn to specific salt types. Applicants therefore request that the rejection of claims 67 and 68 under 35 U.S.C. §112, second paragraph, be withdrawn.

Applicants reiterate the statements made in the foregoing section that it is completely proper and appropriate to claim a narrower scope in a claim (e.g., any of claims 60, 62, 67 and 68) that depends from a broader claim (e.g., claim 59). Like product claim 35, composition claim 59 is drawn to all amounts, types and salts of 3,11b-*cis*-dihydrotetrabenazine. The

language of claim 59, as well as dependent claims 60, 62, 67 and 68, therefore meets the requirements of 35 U.S.C. §112, second paragraph, and Applicants request that these rejections of claims 59, 60, 62, 67 and 68 be withdrawn.

The Rejection of Claims under § 103

The Examiner has made three rejections of the claims under 35 U.S.C. 103(a), asserting *inter alia* that one of skill in the art could predict the structures of Applicants *cis*-isomers from tetrabenazine and its *trans*-isomers that were available in the art. However, for the purpose of determining obviousness, a line drawing of a structure is a mere symbol and is not the compound. Instead, it is the compound itself, with all of its properties, that the Examiner must consider.

> From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. The graphic formulae, the chemical nomenclature, the systems of classification and study such as the concepts of homology, isomerism, etc., are mere symbols by which compounds can be identified, classified, and compared. But a formula is not a compound and while it may serve in a claim to *identify* what is being patented, as the metes and bounds of a deed identify a plot of land, the *thing* that is patented is not the formula but the compound identified by it. And the patentability of the thing does not depend on the similarity of its formula to that of another compound but of the similarity of the former compound to the latter. There is no basis in law for ignoring any property in making such a comparison. An assumed similarity based on a comparison of formulae must give way to evidence that the assumption is erroneous. *In re Papesch*, 137 U.S.P.Q. 43 (CCPA 1963).

Applicants reiterate that the claimed compounds are patentable for at least the following reasons:

1) The invention is based on the development and synthesis of *cis*-dihydrotetrabenazine compounds that did not previously exist in any available form.

2) The prior art teaches no methods by which the compounds of the claims can be obtained.

3) The prior art would guide the skilled person away from making the compounds of the invention because Kilbourn guides the skilled artisan to conclude that the *cis*-isomers may be unstable in view of studies showing that only the *trans*-isomers were

known.

4) Faced with the difficulty of developing new synthetic methods for potentially unstable molecules, the skilled person would have been deterred from making the compounds of the invention. Rather than try to make the *cis*-dihydrotetrabenazine isomers, the skilled person would have been more likely to investigate analogs and derivatives of the *trans*-dihydrotetrabenazine isomers that could be made by well established methods.

5) The compounds of the invention exhibit unexpected benefits and properties that are not predictable from the prior art disclosures relating to the known *trans*-dihydrotetrabenazine isomers. Evidence of the surprising properties of the compounds of the invention is set forth in the patent specification and in a Declaration by Phil Nichols, submitted herewith.

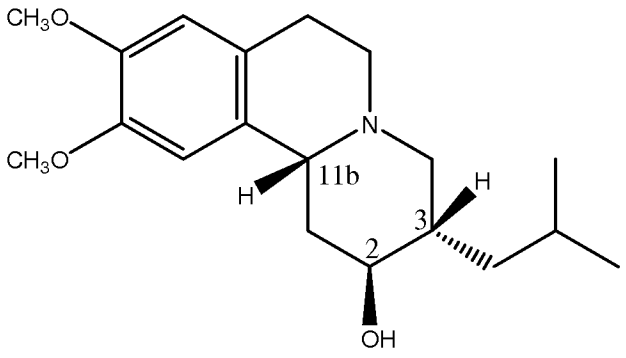
6) The *trans*-dihydrotetrabenazines were first published 46 years before the priority date of the present invention. The fact that the prior art has been silent about the *cis*-dihydrotetrabenazines for such a prolonged period is evidence that the compounds of the present application and methods for making them were not obvious.

The three rejections made by the Examiner are separately addressed in more detail below.

Claims 35, 42 and 58

Claims 35, 42 and 58 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Kilbourn et al. (Eur. J Pharmacol, 278:249-252, 1995; hereinafter "Kilbourn") in view of Williams et al. (Foye's Principles of Medicinal Chemistry, Page 50, 2002; hereinafter "Williams").

Claim 35 is drawn to 3,11b-*cis*-dihydrotetrabenazine or a salt thereof. Claims 42 and 58 depend from claim 35. Claim 42 is directed to a 2*S*,3*S*,11b*R* isomer thereof having the formula (Ia):



(Ia).

Claim 58 is recites that 3,11b-*cis*-dihydrotetrabenazine or a salt thereof consists of greater than 90% 3,11b-*cis*-dihydrotetrabenazine, or a salt thereof.

The Examiner alleges that one of ordinary skill in the art would recognize Applicants' isomers from the Kilbourn disclosure even though Kilbourn does not explicitly disclose Applicant's elected species. According to the Examiner, single isomers are often therapeutically superior to the racemic mixture and to the other isomers, as allegedly taught by Williams. Therefore, the Examiner asserts that it would be obvious to a person of ordinary skill in the art to produce the *2S,3S,*11b*R* isomer recited in Applicants' claims.

However, these arguments fail for at least three reasons. First, prior to Applicants' invention, Applicants' isomers were not available and no one knew how to make them. The combination of Kilbourn and Williams does not cure this defect. Accordingly, it would *not* have been obvious to a person of ordinary skill in the art to produce Applicants' compounds. Second, Kilbourn and Williams teach away from Applicants' compounds because these references instruct those of skill in the art that all the known isomers of tetrabenazine, α-dihydrotetrabenazine and related benzoisoquinolines are *trans* isomers (Kilbourn, page 249, right column). Third, Applicants' *cis* isomers exhibit surprisingly improved properties relative to compounds that were available in the prior art.

The Examiner acknowledges Applicants assertions that "no one of skill in the art could simply purify *cis*-dihydrotetrabenazine isomers from existing preparations of *trans*-dihydrotetrabenazine or tetrabenazine" and that "no one knew how to make the *cis* isomers" but asserts that further evidence is needed to demonstrate that the *cis* isomers could not be made.

Applicants submit that the specification as filed demonstrates that new methods were required to make Applicants' *cis* isomers and that the Kilbourn disclosure expressly discloses that all the known isomers of tetrabenazine, α-dihydrotetrabenazine and related benzoisoquinolines are *trans* isomers (Kilbourn, page 249, right column). Accordingly, Kilbourn explicitly states that the 3,11b-*trans*-dihydrotetrabenazine are made by reduction of tetrabenazine (Kilbourn, page 250, left column) and that "*extensive* NMR studies of tetrabenazine, α-dihydrotetrabenazine and related benzoisoquinolines have *established* the *fixed* relative configurations at the C-3 and C-11b positions" (Kilbourn, page 249, right column). Given that the available starting materials were all *trans* compounds, Applicants had to develop a

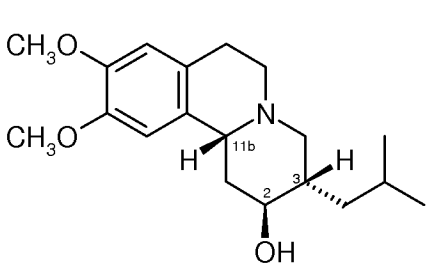
variety of procedures to make and isolate the *cis* isomers, which are described at pages 10-18 and in the Examples of Applicants' specification. Therefore, the combination of Kilbourn and Williams fails to disclose or teach the subject matter of claims 35, 42 and 58 because this combination does not disclose Applicants' *cis* isomers and fails to provide methods for making them.

Kilbourn guides one of skill in the art away from even attempting to make Applicants' *cis* isomers by teaching that *extensive* NMR studies were performed on the available preparations not only of α-dihydrotetrabenazine, but also of tetrabenazine and related benzoisoquinolines, and these studies *established* the *fixed* relative configurations at the C-3 and C-11b positions (page 249, right column). These statements alert one of skill in the art that *cis* isomers at the C-3 and C-11b positions cannot be made in the same way that the *trans* isomers are made, and/or the *cis* isomers are so unstable that the *cis* isomers essentially do not exist. Williams fails to teach anything about dihydrotetrabenazine or its isomers. Therefore, Williams fails to correct the defects of Kilbourn and the combination of Kilbourn and Williams would discourage the skilled artisan from attempting to make the *cis* isomers of Applicant's claims because this combination teaches that the *cis* isomers cannot readily be made.

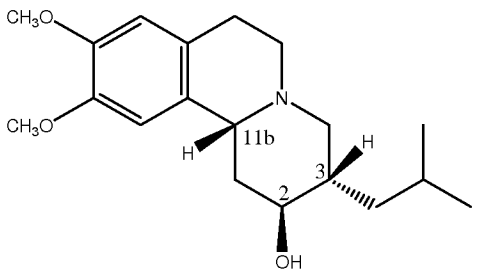
Hence, no one knew that Applicants' *cis* isomers could actually exist and, as described above, no one knew how to make them.

Moreover, the Declaration by Phil Nichols illustrates that Applicants' *cis* isomers have unexpected properties and are therefore a significant advance over the prior art tetrabenazine compound and its *trans*-dihydrotetrabenazine isomers. In particular, the Declaration by Phil Nichols provides evidence that all four *cis*-dihydrotetrabenazine isomers of Applicants' claims were less sedating than tetrabenazine (¶9).

For example, Applicants' B and C *cis*-dihydrotetrabenazine isomers exhibited no sedation at doses of 0.3, 1, 3 & 10 mg/kg, whereas tetrabenazine exhibited sedation in a dose-dependent fashion at both 45 minutes and 3 hours after dosing (Declaration by Phil Nichols, ¶5). As described by Phil Nichols isomer B has the following structure, which is the same as the 2*S*,3*S*,11b*R* isomer of claim 42, which has formula (Ia) (*id.*, ¶5).



Isomer B



Compound Ia (Ia).

Additional studies described by Phil Nichols illustrate the sedation effects of the various *cis*-isomers relative to tetrabenazine. Thus, the combined results of the PF40/1 & PF40/2 studies described in the Declaration by Phil Nichols indicate that tetrabenazine is slightly more sedating than Isomer D, significantly more sedating than Isomer A, and much more sedating than Isomers B and C (¶¶ 9). The experiments described by Phil Nichols therefore indicate that the relative sedating abilities of these compound are in the following order tetrabenazine > Isomer D > Isomer A > Isomers C/B. In other words, all four *cis*-dihydrotetrabenazine isomers of Applicants' application were less sedating than tetrabenazine.

As explained in the previous response submitted by Applicants, tetrabenazine is known to have side effects such as depression, parkinsonism, drowsiness, nervousness or anxiety, insomnia and, in rare cases neuroleptic malignant syndrome[1] and the active metabolite of tetrabenazine, *trans*-dihydrotetrabenazine is responsible for these side effects. This conclusion is supported by the disclosures of earlier documents relating to dihydrotetrabenazines. For example, U.S. Patent 2,843,591[2] discloses that the dihydrotetrabenazines have sedative properties.[3] Sedative properties for dihydrotetrabenazines are also mentioned an article by Brossi *et al.*[4] In contrast, the four compounds of the present invention have been tested as described above and have been found to be less sedating than the prior art compound, tetrabenazine,[5] and therefore its metabolites, the *trans*-dihydrotetrabenazine isomers.

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[1] See, Applicant's specification page 1, lines 17 to 22; see also page 18, line 11 to page 19, line 19.
[2] Provided in the Information Disclosure Statement submitted herewith.
[3] See, U.S. Patent 2,843,591 at col. 2, line 69.
[4] *Helv. Chim. Acta* at 119, 128 (1958); *see* Translation of Brossi article at page 5.
[5] See also, Example 11 of Applicant's specification; and EP Patent Application 05708289.3, Response to Office Action (Sep. 17, 2007)(submitted in an Information Disclosure Statement). Note that EP Patent Application 05708289.3 is the corresponding European patent application.

The non-sedating properties of the compounds of the invention are entirely unexpected in view of the known properties of tetrabenazine and its *trans*-dihydrotetrabenazine metabolites. Such properties are a substantial advance over tetrabenazine and its *trans*-dihydrotetrabenazine metabolites.

Moreover, four compounds of Applicant's claims are essentially inactive against the Dopamine Transporter (DAT) transporter, indicating that Applicant's *cis* isomers do not have the dopaminergic side effects exhibited by tetrabenazine.

> Surprisingly, isomers C and B also show a remarkable separation of VAMT2 and dopamine receptor activity in that although they are highly active in binding VMAT2, both compounds exhibit only weak or non-existent dopamine receptor binding activity and lack Dopamine Transporter (DAT) binding activity. **In fact, none of the isomers exhibit significant DAT binding activity.** This suggests that the compounds may lack the dopaminergic side effects produced by tetrabenazine.[6]

The lack of DAT binding activity of the present compounds is demonstrated by the data in Table 6 of Applicant's specification.[7] As can be seen, each of the four compounds of the invention is essentially inactive against the DAT transporter. Such results could not have been predicted on the basis of the known properties of tetrabenazine and its *trans*-dihydrotetrabenazine active metabolites.

Neither Kilbourn nor Williams disclose any such advantageous properties for dihydrotetrabenazine isomers, or any related compounds. Accordingly, the activities for the *cis* isomers of Applicant's invention are surprising and unexpected. When the therapeutic properties of an enantiomer are unexpected that enantiomer is not obvious in light of the known racemate. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1088 (Fed. Cir. 2008); *Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc.*, 501 F.3d 1263, 1269 (Fed. Cir. 2007). Here, the *cis* isomers of the dihydrotetrabenazine were not even available in any known racemate. However, Applicants' *cis* isomers do have unexpected properties, and no synthetic procedures were available to make Applicants' *cis* isomers relative to prior art compounds. Therefore, the subject matter of Applicants claims is nonobvious in view of the combination of Kilbourn and Williams.

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[6] Applicant's specification at page 18, lines 23-27 (emphasis added).
[7] Applicant's specification at page 49, Table 6, see entry (j).

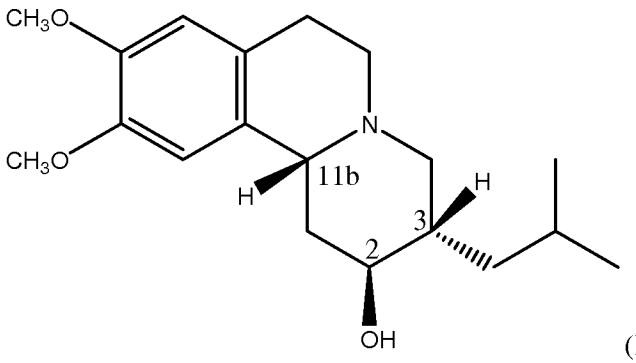
The combination of Kilbourn and Williams therefore fails to disclose or teach the compounds of claims 35, 42 and 58 and Applicants respectfully request withdrawal of this rejection under 35 U.S.C. 103(a).

Claims 36, 38, 39, 49, 59, 60 and 62

Claims 36, 38, 39, 49, 59-60 and 62 have been rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Kilbourn et al. (Eur. J. Pharmacol., 278:249-252, 1995; hereinafter "Kilbourn") as applied to claims 35 and 42 above, in view of Reich et al. (U.S. Patent 6,462,069; hereinafter "Reich").

The Examiner asserts that Reich's teachings on compositions comprising amino-pyrazole compounds combined with Kilbourn's teachings on pharmaceutical compositions comprising a *trans*-dihydrotetrabenazine isomer make Applicants' claims obvious. The Examiner states that Kilbourn teaches pharmaceutical compositions comprising a *trans*-dihydrotetrabenazine isomer that strongly binds VMAT2 and the skilled artisan would therefore have been motivated to formulate pharmaceutical compositions comprising the 2S,3S,llbR *cis* isomer to determine whether it can bind VMAT2 with increased potency and selectivity, decreased side effects, improved onset and duration, reduced drug-drug interactions, etc. as compared to racemic dihydrotetrabenazine or the *trans*-isomers of dihydrotetrabenazine.

Claim 36 is drawn to a composition consisting of 3,11b-*cis*-dihydrotetrabenazine, or a salt thereof, in substantially pure form. Claim 38 is directed to a composition comprising 3,11b-*cis*-dihydrotetrabenazine or a salt thereof, the composition being substantially free of 3,11b-*trans*-dihydrotetrabenazine. Claim 39 is drawn to a composition comprising 3,11b-*cis*-dihydrotetrabenazine or a salt thereof with less than 5% of 3,11b-*trans*-dihydrotetrabenazine. Claim 49 is directed to a pharmaceutical composition comprising 3,11b-*cis*-dihydrotetrabenazine or a salt thereof and a pharmaceutically acceptable carrier. Claim 59 is drawn to a composition comprising 3,11b-*cis*-dihydrotetrabenazine, or a salt thereof, and a pharmaceutically acceptable carrier, wherein the 3,11b-*cis*-dihydrotetrabenazine, or a salt thereof, consists of greater than 90% 3,11b-*cis*-dihydrotetrabenazine, or a salt thereof. Claims 60 and 62 depend from claim 59, and respectively recite that the composition contains less than 5% of 3,11b-*trans*-dihydrotetrabenazine and that the 3,11b-*cis*-dihydrotetrabenazine is a 2*S*,3*S*,11b*R* isomer having the formula (Ia), or a salt thereof:



(Ia).

However, the combination of Kilbourn and Reich fails to disclose Applicants' compositions because that combination fails to teach that Applicants' isomers actually exist, fails to provide methods for making Applicants' isomers and actually guides one of skill in the art away from making Applicants' isomers. As described above, Kilbourn expressly states that commercially available tetrabenazine (as well as all readily available α-dihydrotetrabenazines and benzoisoquinolines) have a fixed (*trans RR* and *SS*) configuration. Therefore, Kilbourn guides one of skill in the art away from even attempting to make Applicants' *cis* isomers. Hence, the prior art alerts one of skill in the art that the *cis* isomers did not exist and that the methods for making related compounds would not yield the *cis*-isomers, thereby indicating that there were problems with making the *cis*-isomers (e.g., essentially no yield or instability).

Moreover, the prior art fails to teach that the specific isomers claimed by Applicants have surprisingly beneficial properties compared to the existing compositions of tetrabenazine and its *trans*-dihydrotetrabenazine metabolites. Thus, the Declaration by Phil Nichols provides evidence that prior art compositions of tetrabenazine are slightly more sedating than Applicants' Isomer D, significantly more sedating than Applicants' Isomer A, and much more sedating than Applicants' Isomers B and C (¶¶ 9). The experiments described by Phil Nichols therefore indicate that all four *cis*-dihydrotetrabenazine isomers of Applicants' application were less sedating than tetrabenazine. Moreover, four compounds of Applicant's claims are essentially inactive against the Dopamine Transporter (DAT) transporter (*see, e.g.*, Table 6 of Applicants' specification, entry (j)), indicating that Applicant's *cis* isomers do not have the dopaminergic side effects exhibited by tetrabenazine. No one of skill in the art could have predicted these beneficial properties from the cited prior art.

Accordingly, the fact that the combination of Kilbourn and Reich teaches compositions of tetrabenazine and/or *trans*-dihydrotetrabenazine compositions is irrelevant. Applicants submit that the data and comments described herein demonstrate that claims 69-71 are patentable over and distinct from the cited art. Clearly, Applicants' compositions did not exist in the prior art, methods to make these compositions were not available and the beneficial properties of Applicants' compositions could not be predicted. Applicants respectfully request withdrawal of this rejection of claims 36, 38-39, 49, 59-60 and 62 under 35 U.S.C. 103(a).

Claims 47, 48, 67 and 68

Claims 47, 48, 67 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilbourn et al. (Eur. J. Pharmacol., 278:249-252, 1995; hereinafter "Kilbourn") as applied to claims 35 and 42 above in view of Berge et al (cited in a previous Action).

Claims 47 and 48 depend ultimately from claim 35 while claims 67 and 68 depend from claim 59. Claims 47 and 67 recite that the 11b-*cis*-dihydrotetrabenazine is in the form of an acid addition salt while claims 48 and 68 define the 3,11b-*cis*-dihydrotetrabenazine salt of claims 47 and 67, respectively, as a methane sulphonate salt.

The deficiencies of Kilbourn are enumerated above. Berge dos nothing to cure these deficiencies.

The Examiner asserts that Berge teaches that "[t]he chemical, biological, physical, and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form" (citing page 1, column 1) and that Berge discloses that methanesulfonic acid is a potentially useful salt form of pharmaceutical agents (citing page 5, Table III). The Examiner therefore alleges that Berge combined with Kilbourn teaches Applicants' compounds and that formulation of compound salts is not so unpredictable as Applicants have asserted.

However, Berge is limited to general information on pharmaceutical salts. Nowhere does Berge mention dihydrotetrabenazine or tetrabenazine, or any isomer thereof. Nowhere does Berge disclose or teach anything whatsoever about salts of dihydrotetrabenazine or tetrabenazine. Therefore, Berge not only fails to cure the defects of Kilbourn but also fails to guide one of skill in the art to the specific salts that are recited in Applicants' claims.

Moreover the table cited by the Examiner (Table III) lists 39 different types of salt forming agents and Berge teaches that that there is no unreliable way of predicting the influence of a particular salt species on the behavior of the parent compound (see, Berge, page 1, right column).

> **Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound. Furthermore, even after many salts of the same basic agent have been prepared, no efficient screening techniques exist to facilitate selection of the salt most likely to exhibit the desired pharmacokinetic, solubility, and formulation profiles.**

Therefore, contrary to the Examiner's allegations Berge actually informs one of skill in the art that no one can predict which salt may be better than any other.

The unpredictability of making salts of Applicants' isomers is compounded by the unpredictability of making the *cis*-isomers themselves. As described above, Kilbourn fails to disclose how Applicants' isomers can be made, and Berge is silent on this issue. Moreover, Kilbourn teaches that all the known isomers of tetrabenazine, α-dihydrotetrabenazine, and related benzoisoquinolines are *trans* isomers,[8] thereby guiding one of skill in the art to the conclusion that *cis* isomers were not easily formed and/or were unstable.

Thus, the motivation to make Applicants' compounds was very low because one of skill in the art faced the uncertainty of not knowing whether he or she could successfully make Applicants' compounds as well as the uncertainty of whether those compounds and their salts would have any beneficial properties. Nor could one of skill in the art predict whether any of Applicants' compounds, or their salts, could avoid negative side effects such as such as depression, parkinsonism, drowsiness, nervousness, anxiety, insomnia or neuroleptic malignant syndrome. See, Applicant's specification page 1, lines 17 to 22; see also page 18, line 11 to page 19, line 19.

This combination of references therefore fails to disclose why one type of isomer and why one salt of that isomer should be selected over another because this combination fails to disclose which isomers and salts exhibit beneficial properties. Only Applicants' invention

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[8] Kilbourn, page 249, right column.

illuminates which isomers and salts are superior, and only Applicants' invention provides the methods for successfully making those superior isomers and, hence, their salts.

Applicants respectfully request withdrawal of this rejection of claims 47-48 and 67-68 under 35 U.S.C. 103(a).

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's representative at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

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John D. Gustav-Wrathall
Name

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Signature